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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/727,355	12/03/2003	Ih-Jen Su	12563-020001	5446

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EXAMINER	
SHIN, DANA H	

ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/727,355	SU ET AL.	
	Examiner	Art Unit	
	Dana Shin	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30,32-35,37-40 and 42* is/are pending in the application.

4a) Of the above claim(s) *1-26,35,40,42 and 360* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-29,32-34 and 37-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

This Office action is in response to the communications filed on and December 21, 2007.

Currently, claims 27-29, 32-34, and 37-39 are under examination on the merits.

The following rejections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

New Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 27, 32, and 37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 27, 32, and 37 recite the limitation "a nucleic acid encoding the RNA" in line 3. There is insufficient antecedent basis for this limitation in the claim, because only the phrase "an RNA or a DNA vector", not "RNA" recited in the phrase "encoding the RNA", antecedes the aforementioned limitation, and therefore, one of ordinary skill in the art would not be able to ascertain which RNA is being claimed to be encoded, thereby rendering the claims indefinite.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 27-29 and 32-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Morrissey et al. (US 2003/0148985 A1) in view of Paul et al. (*Nature Biotechnology,* May 2002, 29:505-508), Stuyver et al. (citation of record), and Linnen et al. (US 2004/0029111 A1).

The claims are drawn to methods of reducing HBV expression and inhibiting viral replication in a cell *in vitro* comprising introducing a DNA vector containing an RNA duplex structure comprising SEQ ID NO:3, which is targeted to HBsAg of HBV gene, wherein the RNA duplex contains a strand that hybridizes under stringent conditions to the targeted segment of the HBV gene.

Morrissey et al. teach a method of inhibiting HBV expression and replication in human cells *in vitro* by introducing nucleic acid inhibitors that bind to HBV genomic sequences, wherein the nucleic acid inhibitors include double-stranded RNAi molecules (paragraphs 0001-0002, 0057, 0059-0061, 0087). They teach that HBV infection in humans is determined by measuring HBsAg in their blood, wherein HBsAg is a surface protein/antigen that envelops a central core antigen (paragraphs 0006, 0013). They teach that the therapies for treating HBV infection available as of December 5, 2001 (their priority filing date) are only partially effective and therefore a need for more effective treatment exists (paragraph 0027). They teach that the anti-HBV nucleic acid molecules are preferably expressed from DNA or RNA vectors (paragraph 0204). They teach that varying substitutions and modifications of the described invention can be made in line with the scope and spirit of the invention and such changes will be apparent to a person of ordinary skill in the art (paragraphs 0235-0236). Morrissey et al. do not teach the claimed sequence of SEQ ID NO:3.

Paul et al. teach that an expression construct comprising an shRNA (short hairpin siRNA) is effective in reducing targeted gene expression in mammalian cells *in vitro*. They teach that preliminary experimental data comprising an expression construct containing an shRNA against

HIV-1 reverse transcriptase coding region have shown that the hairpin siRNA strategy is effective in inhibiting targeted viral gene expression. See page 507.

Stuyver et al. teach a sense amplification and sequencing primer for HBV, which is named "HBPr75 (or SEQ ID NO:75)" and hybridizes to the HBsAg region of HBV. See Table 1. The primer sequence of Stuyver et al. comprises the entire 19 nucleotides of the instantly claimed HBV siRNA sequence of SEQ ID NO:3. See below for nucleotide sequence alignment between the instant SEQ ID NO:3 ("Qy") and SEQ ID NO:75 of Stuyver et al. ("Db").

```
Qy          1 GGTATGTTGCCCGTTTGTC 19
              ||||||||||||||||||
Db          4 GGTATGTTGCCCGTTTGTC 22
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Stuyver et al. teach that the primer comprising SEQ ID NO:75 amplifies the HBsAg region in a PCR amplification. See column 23. They teach, "Protection against HBV infection of all subtypes is conferred by antibodies to the common 'a' determinant of the HB surface antigen (HBsAg)." See column 2, lines 2-4. They teach that the most important region of antigenicity is located between amino acids 124 and 147, which therefore embraces all 19 nucleotides of SEQ ID NO:3 claimed in the instant case. See column 2, line 7 and Figure 1D. Moreover, as Figure 1D illustrates (replicated below), the 19 nucleotides of SEQ ID NO:3 claimed in the instant case are faithfully shared by 35 different HBV genomic sequences, except that there are one or two nucleotide substitutions in three HBV genomic sequences.

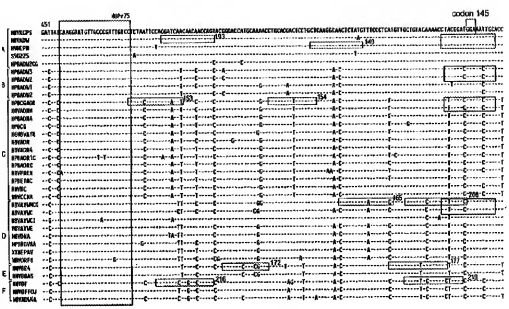

Fig.1D

Concordant with the teachings of Stuyver et al., Linnen et al. teach that a polynucleotide sequence of SEQ ID NO:15 ("GACAAACGGGCAACATACCTT") is used to amplify HBV, wherein the sequence is complementary to the claimed target sequence of SEQ ID NO:3 in the instant case. See paragraph 0071 and Table 1. They teach that the HBV-specific amplification primer of SEQ ID NO:15 was selected because it contains a conserved region of greater than 15 contiguous bases in length, and because of its sensitivity and specificity to hybridize to its complementary sequence such that the polynucleotide sequence of SEQ ID NO:15 distinguishes its target sequence from non-targeted sequences with great thermal stability (paragraphs 0058, 0060, 0064, 0069). They teach that the HBsAg, which can be detected from 2 to 12 weeks after infection with HBV, is the first serologic marker for HBV infection (paragraph 0004).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make an shRNA construct against the surface antigen gene of HBV (HBsAg) in order to inhibit HBV viral replication and its expression in cells *in vitro*.

One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success because the need for a better, more effective HBV inhibition strategy was recognized in the art as taught by Morrissey et al., who also taught that RNAi-mediated HBV inhibition strategy is certainly one of the options that a skilled artisan could further pursue. Since Morrissey et al. further indicated that HBV infection in humans is determined by measuring HBsAg, and since Linnen et al. taught that HBsAg is the first serologic marker for HBV infection, and since Stuyver et al. taught the HBsAg gene of HBV is shared among all subtypes of HBV, one of ordinary skill in the art would have recognized the significant role of HBsAg in mediating HBV infection and therefore would have been motivated to target the HBsAg in order to inhibit the replication/expression of HBV. Hence, in order to inhibit the HBsAg segment of the HBV gene in an effective manner, the skilled artisan would have searched for an optimal target sequence that is shared by as many subtypes (or variants) of the HBV genome as possible, and therefore would have reasonably considered the HBsAg segment that encompasses the claimed sequence of SEQ ID NO:3, which Stuyver et al. taught to be shared and conserved by at least 35 different HBV genomic sequences. Further, the skilled artisan would have been motivated to target this specific region, because two independent research teams found that amplification primers targeted to the specific region embracing the sequence of SEQ ID NO:3 (known as SEQ ID NO:75 in Stuyver et al. and SEQ ID NO:15 in Linnen et al.) hybridize to the conserved HBsAg region of HBV with great sensitivity, specificity, and stability. Having identified the desired target region of the HBsAg segment of HBV, the skilled artisan would have been motivated to design the RNAi molecule as suggested by Paul et al. and produce an expression construct containing an shRNA comprising the claimed sequence of SEQ ID NO:3,

because Paul et al. taught the expression construct comprising an shRNA is effective in inhibiting viral gene expression in cells *in vitro*. Since all the necessary methodologies and knowledge to arrive at the claimed invention were within the technical grasp of one of ordinary skill in the art at the time of the invention, the claimed invention taken as a whole would have been *prima facie* obvious at the time of filing.

Claims 37-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Morrissey et al. (US 2003/0148985 A1) in view of Stuyver et al. (citation of record), Linnen et al. (citation of record), and McCaffrey et al. (*Nature,* July 2002, 418:38-39).

The claims are drawn to a method of treating an HBV infection in a subject, comprising administering to a subject an effective amount of a vector containing an RNA duplex structure comprising SEQ ID NO:3, which is targeted to HBsAg of HBV gene.

The teachings of Morrissey et al., Stuyver et al., and Linnen et al. are described above at pages 3-5. To reiterate, the combined references teach a method of inhibiting HBV expression/replication in a cell *in vitro* by making and using an expression vector containing a short hairpin RNA against one of the well-conserved and highly antigenic regions of the HBsAg gene taught by Stuyver et al. as well as Linnen et al., which is found to coincide with the nucleotide sequence of the claimed SEQ ID NO:3. The combined references do not teach using the shRNA expression vector to treat HBV infection in a subject *in vivo*.

McCaffrey et al. teach that it is feasible to use an expression vector containing an shRNA against HCV, which is a related disease to the claimed HBV, in a living organism *in vivo* as an RNAi therapy and that the shRNA-based strategy can be used to treat human pathogens. See the

entire reference. They specifically state, "These findings indicate that plasmid-encoded shRNAs can induce a potent and specific RNAi response in adult mice...Our method of RNAi delivery could also be tailored to take advantage of developing viral and non-viral gene-transfer vectors in a clinical context." See the last two paragraphs on page 93.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use an expression vector containing a short hairpin RNA against the HBsAg gene in a living organism *in vivo* to treat human HBV-associated diseases.

One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success because RNAi-mediated HBV inhibition was known in the art and because an expression vector containing an shRNA against a human pathogenic gene such as HCV, a closely related pathogen to the instantly targeted HBV, was known to be useful to treat the viral disease via RNAi-mediated gene therapy. Since the utility as well as clinical/therapeutic feasibility of employing an shRNA construct targeted to a hepatitis viral gene as taught by McCaffrey et al., and since the instantly claimed SEQ ID NO:3 was known to be the most conserved, highly antigenic region of the HBV genome, one of ordinary skill in the art would have been motivated to make an shRNA construct containing SEQ ID NO:3 and use it to treat HBV infection in a living subject. Since the knowledge and skills required to arrive at the claimed invention were within the technical grasp of one of ordinary skill in the art at the time of the invention, the instantly claimed invention taken as a whole would have been *prima facie* obvious at the time of filing.

Response to Arguments

Applicant's arguments filed on December 21, 2007 have been fully considered but they are not persuasive. Applicant argues that the claimed invention is unobvious because the claimed DNA vector comprising SEQ ID NO:3 inhibited HBsAg expression by an "unexpected level of 99%", without further elaborating on why such level of inhibition is indeed "unexpected". As pointed out by applicant, page 6 of the specification describes that pSUPER-HBsAg-3 inhibited HBsAg expression level in cells *in vitro* by about 99% based on an ELISA test. However, the specification also teaches that other expression vectors comprising other shRNAs, such as pSUPER-HBsAgs-6, -7, -9, and -10 also inhibited the HBsAg expression by more than 90%. As such, the inhibition level up to about 99% is not at all "unexpected" as alleged by applicant. Further, the ELISA method of assessing alterations in expression level as used to measure the "about 99%" inhibition is a semi-quantitative method because it relies on the change in fluorescence or color. Furthermore, there is no statistical analysis on the significance of the "99%" inhibition. Regardless, since the nucleotide sequence of claimed SEQ ID NO:3 was known to be well-conserved by 35 different HBV genomic sequences unlike other SEQ ID NOs (e.g., pSUPER-HBsAgs-6, -7, -9, and -10), as taught by Stuyver et al, and since the claimed methods expressly recite that the RNA duplex is subject to "stringent conditions" so that the duplex hybridizes to the targeted segment of the gene, a strong level of inhibition on HBsAg expression would have been reasonably expected by any person of ordinary skill in the art at the time of the invention when the HBsAg expression was inhibited by targeting the conserved nucleotide sequence of the different HBV genomic sequences under stringent conditions as claimed in the instant case. Since applicant's alleged unexpected results were not substantiated

by objective, factual evidence, applicant's argument for unobviousness of the claimed invention is found to be unpersuasive.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dana Shin whose telephone number is 571-272-8008. The examiner can normally be reached on Monday through Friday, from 8am-4:30pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Dana Shin
Examiner
Art Unit 1635

/J. E. Angell/
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